Amendments to the Drawings:

Please replace FIGS. 20, 21, 25-29, 31, 32 and 34 with the replacement figures submitted herewith. No changes have been made to the figures; such figures are simply being submitted to bring the drawings into compliance with 37 C.F.R. 1.121(d).

Entry thereof is respectfully requested.

REMARKS

This is meant to be a complete response to the Office Action mailed March 3, 2006. In the Office Action, the Examiner stated that restriction to one of inventions I-V was required under 35 U.S.C. 121, and claims 1-36, 38-75 and 77-101 were objected to because they contain non-elected subject matter. In addition, the Examiner objected to the disclosure and the Sequence Listing. Claims 1-36, 38-75 and 77-101 were rejected under 35 U.S.C. 112, ¶2; claims 1-19, 23-36, 38-56, 60-75, 77-87 and 91-101 were rejected under 35 U.S.C. 112, ¶1 (written description); and claims 1-20, 23-36, 38-57, 60-75, 77-88 and 91-101 were rejected under 35 U.S.C. 112, ¶1 (enablement). Claims 1-5, 10-13, 15-30, 38-42, 47-50, 54-67, 77-81, 85-92 and 101 were rejected under 35 U.S.C. 102(e) as being anticipated by Weigel et al. (US 6,833,264); claims 1-5, 10-13, 15-30, 38-42, 47-50, 54-67, 77-81, 85-92 and 101 were rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over DeAngelis (Biochemistry, 1996, 35:9768-9771); and claims 1-5, 10-13, 15-19, 23-30, 38-42, 47-50, 53-56, 60-67, 77-81, 84-87, 91, 92 and 101 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Triscott et al. (J Biol Chem (1986) 261:6004-6009). In addition, claims 1-20, 23-36, 38-57, 60-75, 77-88 and 91-101 were rejected under obviousness-type double patenting over claims 1-48 of US 6,444,447, and claims 1-20, 23-36, 38-57, 60-75, 77-88 and 91-101 were provisionally rejected under nonstatutory obviousness-type double patenting as being unpatentable over claims 4-10 and 14-19 of allowed copending Application No. 10/197,153 (now US 7,060,469).

Applicant's Response to the Restriction Requirement

In the Office Action, the Examiner stated that restriction to one of the following inventions was required under 35 U.S.C. 121:

I. Claims 1-36, 38-75 and 77-101, drawn to an enzymatic method for the production of glycosaminoglycan polymer using the glycosaminoglycan transferase(sic) of SEQ ID NO:2, classified in class 435, subclass 97.

II. Claims 1-36, 38-75 and 77-101, drawn to an enzymatic method for the production of glycosaminoglycan polymer using the glycosaminoglycan transferase(sic) of SEQ ID NO:4, classified in class 435, subclass 97.

III. Claims 1-36, 38-75 and 77-101, drawn to an enzymatic method for the production of glycosaminoglycan polymer using the glycosaminoglycan transferase(sic) of SEQ ID NO:72, classified in class 435, subclass 97.

IV. Claims 37, 76, 102-106, 108, 110, and 111, drawn to a biopolymer and drug delivery system, classified in class 536, subclass 123.1.

V. Claims 107 and 109, drawn to a method of making pharmaceuticals, classified in class 536, subclass 124.

Applicants respectfully elect Invention I, with traverse. The presently claimed and disclosed invention is directed to an enzymatic method for producing defined glycosaminoglycan polymers that are substantially monodisperse in size, and such enzymatic method is independent of any specific glycosaminoglycan transferase disclosed therein. In fact, the methods of the presently claimed and disclosed invention have been disclosed as utilized with approximately 40 different variations of glycosaminoglycan transferase enzymes, as well as various functional acceptors (including polymerizing one type of polymer backbone onto another type of polymer backbone), thus demonstrating that the methods of the present invention are independent of any specific glycosaminoglycan transferase.

However, for the sake of expediting issuance of a patent from the subject application, the claims have been restricted to Invention I, drawn to an enzymatic method for the production of glycosaminoglycan polymer using the glycosaminoglycan transferase of SEQ ID NO:2, i.e., PmHAS.

Claims 37, 76, 102-106 and 108-111 have been canceled herein, without prejudice, and the remaining independent claims have been amended herein

to recite methods utilizing PmHAS, as well as the truncated and mutated forms disclosed in the application. Below is a Table that outlines such sequences, as well as support in the Specification for activity for such sequences in the methods of the presently claimed invention:

SEQ ID NO:	Truncated/Mutant Form of PmHAS:	Disclosure in Specification:
10	$PmHAS^{1-650}$	Table V
11	$PmHAS^{1-703}$ D477N	Tables VI & IX
12	$PmHAS^{1-703}$ D196N	Tables VI & IX
16	$PmHAS^{1-703}$ D196E	Tables VI & IX
17	$PmHAS^{1-703}$ D196K	Tables VI & IX
18	$PmHAS^{1-703}$ D477E	Tables VI & IX
19	$PmHAS^{1-703}$ D477K	Tables VI & IX
20	$PmHAS^{1-756}$	Tables VIII & V
27	$PmHAS^{46-703}$	[0191]
28	$PmHAS^{72-703}$	[0191]
29	$PmHAS^{96-703}$	[0191]
30	$PmHAS^{118-703}$	[0191]
31	$PmHAS^{1-668}$	[0192]
32	$PmHAS^{1-686}$	[0192]
33	$PmHAS^{1-703}$ D247E	Tables XII & XIII
34	$PmHAS^{1-703}$ D247N	Tables XII & XIII
35	$PmHAS^{1-703}$ D247K	Tables XII & XIII
36	$PmHAS^{1-703}$ D249E	Tables XII & XIII
37	$PmHAS^{1-703}$ D249N	Table XIII
38	$PmHAS^{1-703}$ D249K	Tables XII & XIII
39	$PmHAS^{1-703}$ D527N	Table XIII

SEQ ID NO:	Truncated/Mutant Form of PmHAS:	Disclosure in Specification:
40	$PmHAS^{1-703}$ D527E	Tables XII & XIII
41	$PmHAS^{1-703}$ D527K	Table XII
42	$PmHAS^{1-703}$ D529E	Table XII
43	$PmHAS^{1-703}$ D529N	Table XII
44	$PmHAS^{1-703}$ D529K	Table XII
45	$PmHAS^{1-703}$ E369D	Table XIV
46	$PmHAS^{1-703}$ E369Q	Table XIV
47	$PmHAS^{1-703}$ E369H	Table XIV
48	$PmHAS^{1-703}$ D370E	Table XIV
49	$PmHAS^{1-703}$ D370N	Table XIV
50	$PmHAS^{1-703}$ D370K	Table XIV
71	$PmHAS^{1-703}$	Table XIII; [0032]

It is respectfully submitted that Applicants are entitled to pursue not only the PmHAS sequences disclosed herein, but also the active truncated and mutated forms thereof that are also disclosed in the subject application. Thus, Applicants respectfully submit that the claims as currently pending are only directed to a single invention, and therefore should be considered in a single application.

Applicants' Response to the Objections to the Disclosure, Drawings and Sequence Listing

In the Office Action, the Examiner objected to the Specification and Sequence Listing, and stated in particular that the figure descriptions of Figures 10-19 and 30 contained sequences that were not identified by a sequence identifier.

In response, a substitute Sequence Listing is submitted herewith, and the Specification has been amended herein to fully comply with the requirements of 37 C.F.R. 1.821-1.825. However, Applicants respectfully traverse the rejection as applicable to Figure 30: the letters utilized in the description of Figure 30 refer to polymers, not amino acids; the Examiner's attention is directed to paragraph [0269] of the published application, which clearly demonstrates that the abbreviation CSA, CSB, and CSC are three different chondroitin sulfates, while HA refers to hyaluronic acid. Therefore, no sequence identifiers should be assigned to the abbreviations in Figure 30.

Applicants respectfully submit that no substantive changes have been made to the application, and that such amendments do not constitute new matter. Entry of the substitute Sequence Listing and amendments to the Specification is respectfully requested.

Also in the Office Action, the Examiner stated that new corrected drawings of FIGS. 20, 21, 25-29, 31, 32 and 34 were required in compliance with 37 C.F.R. 1.121(d).

In response, replacement FIGS. 20, 21, 25-29, 31, 32 and 34 are filed herewith. Applicants respectfully submit that such replacement figures fully comply with 37 C.F.R. 1.121(d). No marked up versions of the figures are submitted herewith, as no changes have been made to the figures; the replacement figures simply provide greater detail of the agarose gels shown therein.

Further, the Examiner also stated in the Office Action that the disclosure was objected to because of the following informality: "the phrase 'contains 25, 100' at page 4, last line in paragraph 16, should be ---contains 20-100—". Applicant respectfully traverses the objection, but for the sake of expediting issuance of a patent from the subject application, such amendment to the Specification has been made herein.

Applicants' Response to the 35 U.S.C. 112, ¶2 Rejection

In the Office Action, the Examiner rejected claims 1-36, 38-75 and 77-101 under 35 U.S.C. 112, ¶2, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner provided reasons (a) - (i) for the rejections. Each rejection is addressed herein below.

Regarding (a), Applicants respectfully traverse the rejection. Since the claims were limited in response to the traversed restriction requirement to a hyaluronan synthase, the claim has also been amended to only recite the two sugars added by HAS, or structural variants or derivatives thereof. However, Applicants respectfully submit that the phrase "defined glycosaminoglycan polymer" is definite and particularly points out and distinctly claims the subject matter which Applicants regard as the invention. The functional acceptor may be any polymer backbone, and therefore the defined glycosaminoglycan polymer produced by the method of the presently claimed invention may be a hybrid or chimera of two or more polymer backbones (as recited in dependent claims and as fully enabled by the Specification). Therefore, Applicants respectfully submit that the product produced by the method of the presently claimed invention is a "defined glycosaminoglycan polymer", rather than simply "hyaluronan".

Regarding (b), the phrase "glycosaminoglycan-like" has been replaced with "glycosaminoglycan".

Regarding (c), Applicants respectfully traverse the rejection. Structural variants and derivatives of uronic acid and hexosamine are fully known to a person having ordinary skill in the art. Therefore, Applicants respectfully submit that this term does not render the claims indefinite.

Regarding (d), the cited abbreviations have been defined at their initial usage in the claims.

Regarding (e), the term "heparosan-like" has been amended to "heparin, heparan or heparosan polymer" in claim 9. Claim 46 has been canceled herein, and Applicants are unsure why claim 101 was included in this rejection, as the term "heparosan-like" does not appear in such claim. Claims 31 and 93 have been amended herein to recite "comprising more than one type of polymer backbone" (claims 46 and 68 were canceled herein); support for such amendment can be found in paragraph [0035] of the published application.

Regarding (f), claim 11 has been canceled herein, without prejudice. Applicants are unsure why claim 101 was included in this rejection, as the term "active fragment and mutant thereof" was not included in claim 101. The Examiner's rejection of claims 31, 46, 68 and 93 is a duplicate of that included in (e), and such rejection was addressed herein above.

Regarding (g), claims 20, 57 and 88 have been canceled herein, without prejudice.

Regarding (h), claims 74-75 and 99-100 have been amended herein to recite "having a molecular weight less/greater than about 0.5 MDa".

Regarding (i), Applicants respectfully submit that the rejections of the claims from which claims 6-8, 12, 16-19, 21-30, 32-36, 79, 83-87, 89-92 and 94-98 depend have been overcome.

Therefore, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 112, ¶2 rejection of claims 1-10, 13, 15-19, 23-26, 29-36, 74-75, 77-78, 81, 83-87, and 91-101, as now pending.

Applicants' Response to the 35 U.S.C. 112, ¶1 Rejection(Written Description)

In the Office Action, the Examiner rejected Applicants' claims 1-19, 23-36, 38-56, 60-75, 77-87 and 91-101 under 35 U.S.C. 112, ¶1 (written description).

Applicants respectfully submit that the amendments required in response to the traversed restriction requirement render the 35 U.S.C. 112, ¶1 (written description) rejection moot; however, Applicants respectfully traverse the rejection as related to the originally filed claims, as well as its applicability to the currently pending claims.

The Examiner asserts that Applicants have only disclosed a single representative species of hyaluronan synthase and a truncated version thereof, and that "the specification also fails to describe additional representative species of these hyaluronic acid synthase (HAS) by any identifying structural characteristics or properties other than the amino acid sequence recited in claim 21 (SEQ ID NO:2) or the polypeptide encoding by the nucleic acid sequence of SEQ ID NO:1 of claim 20, for which no predictability of structure is apparent."

This assertion is incorrect; the Specification of the subject application provides a total of **37** different mutants of HAS, and based on these mutants, adequately provides the ability to map the single transferase activities of HAS (as evidenced by 26 of these 37 mutants, which maintained one transferase activity but not the other), as well as conclude which portions of the protein were essential for activity (as evidenced by the 26 single transferase activity mutants and the four null mutants). In addition, the Specification also discloses a second glycosaminoglycan transferase, PmCS, as well as mutants and truncations thereof; further, the Specification even discloses chimeric or hybrid glycosaminoglycan transferases that comprise one or more fragments of each of PmHAS AND PmCS.

Therefore, Applicants respectfully submit that the claims as pending fully comply with the written description requirement of 35 U.S.C. 112, ¶1.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 112, ¶1 rejection of claims 1-10, 13, 15-19, 23-26, 29-36, 74-75, 77-78, 81, 83-87, 91-101, as now pending.

Applicants' Response to the 35 U.S.C. 112, ¶1 Rejection (Enablement)

In the Office Action, the Examiner rejected Applicants' claims 1-20, 23-36, 38-57, 60-75, 77-88 and 91-101 under 35 U.S.C. 112, ¶1 (enablement).

Applicants respectfully traverse the rejection as applicable to the claims as now pending for the reasons stated above in response to the 35 U.S.C. 112, ¶1 (written description) rejection. As stated above, the Specification of the subject application provides a total of **37** different mutants of HAS, and based on these mutants, adequately provides the ability to map the single transferase activities of HAS (as evidenced by 26 of these 37 mutants, which maintained one transferase activity but not the other), as well as conclude which portions of the protein were essential for activity (as evidenced by the 26 single transferase activity mutants and the four null mutants). In addition, the Specification also discloses a second glycosaminoglycan transferase, PmCS, as well as mutants and truncations thereof; further, the Specification even discloses chimeric or hybrid glycosaminoglycan transferases that comprise one or more fragments of each of PmHAS AND PmCS. Such disclosure would fully enable a person having ordinary skill in the art to identify other hyaluronan synthases, as well as mutants, truncations and hybrids/chimeras thereof without undue experimentation.

Therefore, Applicants respectfully submit that the claims as pending fully comply with the enablement requirement of 35 U.S.C. 112, ¶1. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 112, ¶1 (enablement) rejection of claims 1-10, 13, 15-19, 23-26, 29-36, 74-75, 77-78, 81, 83-87, 91-101, as now pending.

Applicants' Response to the Prior Art Rejections

In the Office Action, the Examiner rejected: (a) Applicants' claims 1-5, 10-13, 15-30, 38-42, 47-50, 54-67, 77-81, 85-92 and 101 under 35 U.S.C.

102(e) as being anticipated by Weigel et al. (US 6,833,264); (b) claims 1-5, 10-13, 15-30, 38-42, 47-50, 54-67, 77-81, 85-92 and 101 under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over DeAngelis (Biochemistry, 1996, 35:9768-9771); and (c) claims 1-5, 10-13, 15-19, 23-30, 38-42, 47-50, 53-56, 60-67, 77-81, 84-87, 91, 92 and 101 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Triscott et al. (J Biol Chem (1986) 261:6004-6009).

Applicants respectfully traverse all of the above-referenced rejections, in combination, for the reasons stated herein below.

The claims of the subject application are directed to a method for enzymatically producing defined glycosaminoglycan polymers having a desired size distribution such that the glycosaminoglycan polymers are **substantially monodisperse** in size such that the glycosaminoglycan polymers have a **polydispersity value in a range of from 1.0 to 1.2** (for the Examiner's information, polydispersity values are a unitless entity, as they are Mw/Mn; Daltons/Daltons).

All of the references cited by the Examiner are related simply to the identification of hyaluronate synthases, and do not teach, disclose or even suggest utilizing hyaluronate synthases to produce glycosaminoglycan polymers that are **substantially monodisperse** in size.

In fact, the prior art actually taught that glycosaminoglycan transferases only produce polydisperse products, and thus teach away from the ability to produce monodisperse products. Attached hereto as Exhibits A-E are references that clearly demonstrate the knowledge in the art prior to the presently claimed invention, and thus demonstrate that the prior art actually taught away from monodisperse products produced by glycosaminoglycan transferases. Exhibits A-D are references published prior to the filing of the

subject application, and such prior art references disclose that polysaccharides were known to be polydisperse; Exhibit E was published after the filing date of the subject application, and discloses that hyaluronan was typically known to be polydisperse, and references the presently claimed and disclosed invention as being the first to demonstrate the ability to produce monodisperse hyaluronan (see Page 55, ¶2 and Figure 7).

Thus, the presently claimed and disclosed invention is the first to demonstrate the ability to produce substantially monodisperse products using glycosaminoglycan transferases. The table below illustrates the results obtained with the presently claimed and disclosed invention:

TABLE: Monodisperse HA Characterization as determined by SEC-MALLS* (average of duplicates)

Sample #	Average molecular mass (Mw)	Polydispersity (Mw/M)
1	284 kDa	1.001
2	347 kDa	1.002
3	424 kDa	1.004
4	493 kDa	1.006
5	571 kDa	1.002
6	990 kDa	1.001
7	964 kDa	1.002
8	1,148 kDa	1.007
9	2,000 kDa	1.06

(note: for an ideal polymer, polydispersity = 1)
* Size Exclusion Chromatography -MultiAngle Laser Light Scattering

Portions of the data of the above Table are presented in FIG. 26 of the subject application. In addition, the Examiner's attention is also directed to FIG. 33 and paragraphs [00079] and [000273] of the Specification of the subject application. In FIG. 33, an HA functional acceptor is extended with

chondroitin chains using PmCS; the product had a Mw of 280,000 and a polydispersity value of **1.003**. Also in FIG. 33, a chondroitin sulfate functional acceptor was extended with HA chains using PmHAS; the product had a Mw of 427,000 and a polydispersity value of **1.006**.

These results demonstrate the ability not only to extend HA chains to provide a monodisperse product, but also to create chimeric or hybrid glycosaminoglycan products that are also monodisperse.

Therefore, Applicants respectfully submit that none of the prior art references cited by the Examiner teach, disclose or even suggest methods of producing a defined glycosaminoglycan that is substantially monodisperse, as recited by the pending claims of the subject application.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 102(e) rejection of claims 1-5, 10-13, 15-30, 38-42, 47-50, 54-67, 77-81, 85-92 and 101 as being anticipated by Weigel et al. (US 6,833,264); the 35 U.S.C. 102(b) rejection of claims 1-5, 10-13, 15-30, 38-42, 47-50, 54-67, 77-81, 85-92 and 101 as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over DeAngelis (Biochemistry, 1996, 35:9768-9771); and the 35 U.S.C. 102(b) rejection of claims 1-5, 10-13, 15-19, 23-30, 38-42, 47-50, 53-56, 60-67, 77-81, 84-87, 91, 92 and 101 as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Triscott et al. (J Biol Chem (1986) 261:6004-6009).

Applicants' Response to the Obviousness-Type Double Patenting Rejection

In the Office Action, the Examiner rejected Applicants' claims 1-20, 23-36, 38-57, 60-75, 77-88 and 91-101 under obviousness-type double patenting over claims 1-48 of US 6,444,447; in addition, the Examiner provisionally rejected Applicants' claims 1-20, 23-36, 38-57, 60-75, 77-88 and 91-101 under nonstatutory obviousness-type double patenting as being unpatentable over

claims 4-10 and 14-19 of allowed copending Application No. 10/197,153 (now US 7,060,469).

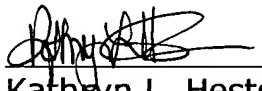
In response to the rejection, a Terminal Disclaimer is being filed herewith which complies with each and every provision of 37 C.F.R. §1.321 and 37 C.F.R. §1.130(b) and which disclaims the terminal portion of any patent granted on this application which would extend beyond the expiration date of US 6,444,447 or US 7,060,469. Applicant respectfully submits that the double-patenting rejections of the claims as now pending have been obviated by the filing of the Terminal Disclaimer and requests reconsideration and withdrawal of such rejection of the claims.

CONCLUSION

This is meant to be a complete response to the Office Action mailed March 3, 2006. Applicants respectfully submit that each and every rejection of the claims has been overcome or obviated by the filing of the Terminal Disclaimer herewith. Further, Applicants respectfully submit that the claims as now pending are patentable over the art of record and are in a condition for allowance. Favorable action is respectfully solicited.

Should the Examiner have any questions regarding this Amendment or the Remarks contained therein, Applicants' agent would welcome the opportunity to discuss the same with the Examiner.

Respectfully submitted,



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